BIRTH DEFECT RISK FACTOR SERIES: PATENT DUCTUS ARTERIOSUS

DESCRIPTION

Patent ductus arteriosus (PDA) occurs as a result of persistence into the postnatal period of the normal fetal vessel (ductus arteriosus) that connects the left pulmonary artery and the aorta. The ductus arteriosus normally closes shortly after birth in normal infants and is considered normal in preterm infants. PDA may also be called persistent ductus arteriosus.

PDA accounts for 2%-15% of all congenital heart defects (Becker et al., 2001; Botto et al., 2001; Borgmann et al., 1999; Samanek and Voriskova, 1999; Jaiyesimi, 1993; Kidd et al., 1993; Fixler et al., 1990; Stoll et al., 1989; Grabitz et al., 1988; Ferencz et al., 1985).

ASSOCIATED BIRTH DEFECTS

Approximately 28%-88% of PDA cases have other cardiac and non-cardiac birth defects (Ferencz et al., 1997; Stoll et al., 1993; Castilla and Lopez-Camelo, 1990), and 8%-11% of cases with PDA also have a chromosomal abnormality (Ferencz et al., 1997; Stoll et al., 1989). PDA is associated with trisomy 21, where PDA can account for 4% of all associated congenital heart defects (Kallen et al., 1996). PDA has also been found with trisomy 18, trisomy 13, Char syndrome, Noonan syndrome, Holt-Oram syndrome, Meckel-Gruber syndrome, and congenital rubella syndrome (Goldmuntz, 2001; Torfs and Christianson, 1998; Webster, 1998; Ferencz et al., 1997). PDA occurs among patients with the 22q11 deletion linked to DiGeorge syndrome, velo-cardio-facial syndrome, and several other syndromes (Borgmann et al., 1999).

PRENATAL DIAGNOSIS

PDA may be identified by prenatal ultrasound and fetal echocardiography. However, the ductus arteriosus is a normal condition among fetuses.

PREGNANCY OUTCOME

The mortality rate associated with PDA has declined in the United States during 1979-1997 (Boneva et al., 2001; Lee et al., 2001). One study noted that 4% of infants with isolated PDA expired within the first year of life (Ferencz et al., 1997).

DEMOGRAPHIC AND REPRODUCTIVE FACTORS

Race/Ethnicity

Studies of risk of PDA by race/ethnicity have been inconsistent (Table 2). While some studies have reported higher rates of PDA among African-Americans than among whites (Botto et al., 2001; Ferencz et al., 1997; Chavez et al., 1988), other investigations found no such difference in PDA rates (Fixler et al., 1993; Correa-Villansenor et al., 1991). PDA rates among Hispanics tend to be lower than among whites and African-Americans (Fixler et al., 1993; Chavez et al., 1988).

Secular and Seasonal Trends

PDA rates have increased over the last several decades (Botto et al., 2001; Ferencz et al., 1997; Anderson et al., 1978). Generally this increase has been attributed to increased use of echocardiography.

Investigation of PDA and seasonality have produced mixed results. One study found no seasonal variation in PDA rates (Tikkanen and Heinonen, 1991) while other studies did report seasonal variation (Samanek et al., 1991a; Bound et al., 1989). Another investigation observed rates for isolated PDA to be lowest in January-March and highest in October-December (Ferencz et al., 1997).

Geography

One study noted isolated PDA to be more common in urban areas (Ferencz et al., 1997). A study in Czechoslovakia reported regional differences in rates of PDA (Samanek et al., 1991b). PDA risk increases with high altitudes (Olley, 1987; Alzamora-Castro et al., 1960).

Sex

PDA is more common among females than among males (Ferencz et al., 1997; Samanek, 1994; Sampayo and Pinto, 1994; Fyler, 1980; Rothman and Fyler, 1976), although one investigation reported 53% of the PDA cases to be among males (Lary and

Paulozzi, 2001).

Parity
One study noted isolated PDA not to be associated with the mother's number of previous pregnancies (Ferencz et al., 1997). Another study reported PDA risk to decrease with increasing birth order (Rothman and Fyler, 1976).

Plurality
Several investigations reported increased risk of PDA among twins (Doyle et al., 1991; Layde et al., 1980) while a more recent study found no association between isolated PDA risk and twins (Ferencz et al., 1997).

Gestational Age and Birth Weight
As noted previously, PDA is associated with preterm delivery, where PDA generally is not considered to be a birth defect. However, among term births isolated PDA risk is associated with lower birth weight (Ferencz et al., 1997). And PDA risk is associated with small for gestational age (intrauterine growth retardation) (Ferencz et al., 1997; Khoury et al., 1988).

Consanguinity
One investigation reported no increased risk of PDA among the offspring born to first cousins (Becker et al., 2001).

Parental Age
Several studies observed decreased risk of PDA with increasing maternal age (Baird et al., 1991; Rothman and Fyler, 1976). However, another study noted no association between isolated PDA and maternal or paternal age (Ferencz et al., 1997).

FACTORS IN LIFESTYLE OR ENVIRONMENT

Socioeconomic Status (SES)
An investigation noted increased risk of isolated PDA with low maternal and paternal education. However, annual household income was not related to isolated PDA risk (Ferencz et al., 1997).

Maternal Illnesses and Conditions
PDA risk increases with maternal diabetes (Loffredo et al., 2001; Ferencz et al., 1997; Becerra et al., 1990). PDA has been reported among the offspring of mothers with phenylketonuria (Levy et al., 2001). There is no association between PDA and maternal hypothyroidism (Khoury et al., 1989), hyperthyroidism (Khoury et al., 1989), or influenza (Ferencz et al., 1997).

In a study that examined the relationship between PDA and maternal hyperthermia, PDA risk was associated with fever and upper respiratory infection but not with workplace temperature or sauna bathing (Tikkanen and Heinonen, 1991).

Maternal Exposures
PDA has not been associated with maternal ampicillin use (Czeizel et al., 2001). Maternal alcohol use does not appear to increase risk of isolated PDA (Ferencz et al., 1997). Although one investigation reported increased risk of PDA with maternal smoking (Kallen, 1999), several other studies found no such association (Ferencz et al., 1997; Van Den Eeden et al., 1990).

Other Exposures
One study observed increased risk of isolated PDA with paternal occupation of clerical/sales (Ferencz et al., 1997). A recent review article reported increased risk of PDA with paternal occupations of painter, plywood mill worker, and sheet and other metal worker (Chia and Shi, 2002).

PREVALENCE

The reported prevalence for PDA has shown wide variation between studies, ranging between 0.9 and 20.6 per 10,000 births (Table 1). There are various potential reasons for the differences in prevalence. Infants with PDA may be asymptomatic. One study observed that 26% of infants undergoing echocardiography solely because of heart murmur had a PDA (Rein et al., 2000). Another study found that 60% of infants with innocent heart murmurs and 12% of infants without heart murmurs had a PDA (Arlettaz et al., 1998).

Differences in prevalence may also be due to differences in case inclusion criteria or the use of echocardiography among the study populations. Studies may differ in their definitions of preterm, i.e., use different gestational age limits or base the limit on birth weight, and some investigations may not exclude preterm infants at all.

Table 1. Prevalence per 10,000 births of patent ductus arteriosus

Reference	Location	Time period	Rate
Botto et al., 2001	Atlanta	1968-1997	6.6
Wren et al., 2000	Great Britain	1985-1997	2.3
Samanek and Voriskova, 1999	Czechoslovakia	1980-1990	3.1
Ferencz et al., 1997	Maryland/Virginia/DC	1981-1989	5.6
Kidd et al., 1993	Australia	1981-1984	1.2
Baird et al., 1991	British Columbia	1966-1981	20.6
Samanek et al., 1991b	Czechoslovakia	1977-1984	3.8
Castilla and Lopez-Camelo, 1990	South America	1982-1986	1.0
Bound et al., 1989	Great Britain	1957-1981	3.4
Stoll et al., 1989	France	1979-1986	6.9
Grabitz et al., 1988	Alberta	1981-1984	1.9
Ferencz et al., 1985	Maryland/Virginia/DC	1981-1982	0.9
Czeizel and Vitez, 1981	Hungary	1970-1977	8.6

Table 2. Prevalence per 10,000 births of patent ductus arteriosus by race/ethnicity

Reference	White	African-American	Hispanic	Native American	Asian
Botto et al., 2001	5.93	7.62			
Fixler et al., 1993	3.6	3.4	2.8		
Chavez et al., 1988	26.5	49.9	20.7	33.5	25.1

REFERENCES

Alzamora-Castro V, Battilana G, Abugattas R, Sialar S. Patent ductus arteriosus and high altitude. Am J Cardiol 1960;5:761-763.

Anderson CE, Edmonds LD, Erickson JD. Patent ductus arteriosus and ventricular septal defect: trends in reported frequency. Am J Epidemiol 1978;107:281-289.

Arlettaz R, Archer N, Wilkinson AR. Natural history of innocent heart murmurs in newborn babies: controlled echocardiographic study. Arch Dis Child Fetal Neonatal Ed. 1998;78:F166-F170.

Baird PA, Sadovnick AD, Yee IM. Maternal age and birth defects: a population study. Lancet 1991;337:527-530.

Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. Pediatrics 1990;85:1-9.

Becker SM, Al Halees Z, Molina C, Paterson RM. Consanguinity and congenital heart disease in Saudi Arabia. Am J Med Genet 2001;99:8-13.

Boneva RS, Botto LD, Moore CA, Yang Q, Correa A, Erickson JD. Mortality associated with congenital heart defects in the United States: trends and racial disparities, 1979-1997. Circulation. 2001;103:2376-2381.

Borgmann S, Luhmer I, Arslan-Kirchner M, Kallfelz HC, Schmidtke J. A search for chromosome 22q11.2 deletions in a series of 176 consecutively catheterized patients with congenital heart disease: no evidence for deletions in nonsyndromic patients. Eur J Pediatr 1999;158:958-963.

Botto LD, Correa A, Erickson JD. Racial and temporal variations in the prevalence of heart defects. Pediatrics 2001;107:e32.

Bound JP, Harvey PW, Francis BJ. Seasonal prevalence of major congenital malformations in the Fylde of Lancashire 1957-1981. J Epidemiol Community Health 1989;43:330-342.

Castilla EE, Lopez-Camelo JS. The surveillance of birth defects in South America. In: *Advances in Mutagenesis Research*. Springer-Verlag, New York. 1990 pp. 191-210.

Chavez GF, Cordero JF, Becerra JE. Leading major congenital malformations among minority groups in the United States, 1981-1986. Mor Mortal Wkly Rep CDC Surveill Summ 1988;37:17-24.

Chia SE, Shi LM. Review of recent epidemiological studies on paternal occupations and birth defects. Occup Environ Med. 2002;59:149-155.

Correa-Villansenor A, McCarter R, Downing J, Ferencz C, Baltimore-Washington Infant Study Group. White-black differences in cardiovascular malformation in infancy and socioeconomic factors. Am J Epidemiol 1991;134:393-402.

Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. A population-based case-control teratologic study of ampicillin treatment during pregnancy. Am J Obstet Gynecol 2001;185:140-147.

Czeizel A, Vitez M. Birth prevalence of five congenital abnormalities of medium frequency in Budapest. Acta Paediatr Acad Sci Hung 1981;22:299-308.

Doyle PE, Beral V, Botting B, Wale CJ. Congenital malformations in twins in England and Wales. J Epidemiol Community Health 1991;45:43-48.

Ferencz C, Rubin JD, McCarter RJ, Brenner JI, Neill CA, Perry LW, Hepner SI, Downing JW. Congenital heart disease: prevalence at livebirth. Am J Epidemiol 1985;121:31-36.

Ferencz C, Loffredo CA, Correa-Villasenor A, Wilson PD, eds. Patent arterial duct. In: *Genetic and Environmental Risk Factors of Major Cardiovascular Malformations: The Baltimore-Washington Infant Study 1981-1989*. Armonk, NY: Fuytura Publishing Co., Inc; 1997: pp. 285-299.

Fixler DE, Pastor P, Chamberlin M, Sigman E, Eifler CW. Trends in congenital heart disease in Dallas County births. 1971-1984. Circulation 1990;81:137-142.

Fixler DE, Pastor P, Sigman E, Eifler CW. Ethnicity and socioeconomic status: Impact on the diagnosis of congenital heart disease. J Am Coll Cardiol 1993;21:1722-1726.

Fyler DC. Report f the New England Regional Infant Cardiac Program. Pediatrics 1980;65:375-461.

Goldmuntz E. The epidemiology and genetics of congenital heart disease. Clin Perinatol 2001;28:1-10.

Grabitz RG, Joffres MR, Collins-Nakai RL. Congenital heart disease: incidence in the first year of life. The Alberta Heritage Pediatric Cardiology Program. Am J Epidemiol 1988;128:381-388.

Jaiyesimi F. Pattern of congenital heart disease in King Fahd Specialist Hospital. Ann Saudi Med 1993;13:407-411.

Kallen B, Mastroiacovo P, Robert E. Major congenital malformations in Down syndrome. Am J Med Genet 1996;65:160-166.

Kallen K. Maternal smoking and congenital heart defects. Eur J Epidemiol 1999;15:731-737.

Khoury MJ, Becerra JE, d'Almada PJ. Maternal thyroid disease and risk of birth defects in offspring: a population-based case-control study. Paediatr Perinat Epidemiol 1989;3:402-420.

Khoury MJ, Erickson JD, Cordero JF, McCarthy BJ. Congenital malformations and intrauterine growth retardation: a population study. Pediatrics 1988;82:83-90.

Kidd SA, Lancaster PA, McCredie RM. The incidence of congenital heart defects in the first year of life. J Paediatr Child Health 1993;29:344-349.

Lary JM, Paulozzi LJ. Sex differences in the prevalence of human birth defects: a population-based study. Teratology 2001;64:237-251.

Layde PM, Erickson JD, Falek A, McCarthy BJ. Congenital malformation in twins. Am J Hum Genet 1980;32:69-78.

Lee K, Khoshnood B, Chen L, Wall SN, Cromie WJ, Mittendorf RL. Infant mortality from congenital malformations in the United States, 1970-1997. Obstet Gynecol 2001;98:620-627.

Levy HL, Guldberg P, Guttler F, Hanley WB, Matalon R, Rouse BM, Trefz F, Azen C, Allred EN, de la Cruz F, Koch R. Congenital heart disease in maternal phenylketonuria: report from the Maternal PKU Collaborative Study. Pediatr Res 2001;49:636-642.

Loffredo CA, Wilson PD, Ferencz C. Maternal diabetes: An independent risk factor for major cardiovascular malformations with increased mortality of affected infants. Teratology 2001;64:98-106.

Olley PM. The ductus arteriosus, its persistence and its patency. In: Anderson RH, Shinebourne EA, Macartney FJ, Tynan M (eds.). *Paediatric Cardiology.* Edinburgh: Churchill Livingstone; 1987:pp. 931-958.

Rein AJ, Omokhodion SI, Nir A. Significance of a cardiac murmur as the sole clinical sign in the newborn. Clin Pediatr (Phila) 2000;39:511-520.

Rothman KJ, Fyler DC. Sex, birth order, and maternal age characteristics of infants with congenital heart defects. Am J Epidemiol 1976;104:527-534.

Samanek M, Slavik Z, Krejcir M. Seasonal differences in the incidence of congenital heart defects. Czech Med 1991a;14:146-155.

Samanek M, Slavik Z, Balatka J, Bartakova H, Goetzova J, Homola J, Rusava I, Smrcka J, Krejcir M. Krajove rozdily vyskytu vrozenych srdecnich vad. Cesk Pediatr 1991b;46:65-70.

Samanek M. Boy:girl ratio in children born with different forms of cardiac malformation: a population-based study. Pediatr Cardiol 1994;15:53-57.

Samanek M, Voriskova M. Congenital heart disease among 815,569 children born between 1980 and 1990 and their 15-year survival: a prospective Bohemia survival study. Pediatr Cardiol 1999;20:411-417.

Sampayo F, Pinto FF. Distribuicao por sexos das cardiopatias congenitas. Acta Med Port 1994;7:413-418.

Stoll C, Alembik Y, Dott B, Roth PM, De Geeter B. Evaluation of prenatal diagnosis of congenital heart disease. Prenat Diagn 1993;13:453-461.

Stoll C, Alembik Y, Roth MP, Dott B, De Geeter B. Risk factors in congenital heart disease. Eur J Epidemiol 1989;5:382-391.

Tikkanen J, Heinonen OP. Maternal hyperthermia during pregnancy and cardiovascular malformations in the offspring. Eur J Epidemiol 1991;7:628-635.

Torfs CP, Christianson RE. Anomalies in Down syndrome individuals in a large population-based registry. Am J Med Genet 1998;77:431-438.

Van Den Eeden, SK, Karagas MR, Daling JR, Vaughan TL. A case-control study of maternal smoking and congenital malformations. Paediatr Perinat Epidemiol 1990;4:147-155.

Webster W. Teratogen update: congenital rubella. Teratology 1998;58:13-23.

Wren C, Richmond S, Donaldson L. Temporal variability in birth prevalence of cardiovascular malformations. Heart 2000;83:414-419.

Please Note: *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information.*

This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.
